Dietary Sodium, Aldosterone, and Left Ventricular Mass Changes During Long-Term Inhibition of the Renin-Angiotensin System

Guilhem du Cailar, Pierre Fesler, Jean Ribstein, Albert Mimran

Abstract—In essential hypertension, the regression of left ventricular hypertrophy is an important goal of treatment. In addition to treatment-associated changes in blood pressure (BP), the roles of other determinants of left ventricular hypertrophy regression, including dietary sodium intake, deserve investigation. In the present study, the change in echographic left ventricular mass index (LVM) was assessed in 182 patients with never-treated essential hypertension at baseline and after 3 years of treatment by angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists given at recommended doses and associated with other antihypertensive agents. Treatment was associated with satisfactory control of BP (<140/90 mm Hg) in 64% of patients, and left ventricular hypertrophy prevalence decreased from 56% to 39%. Twenty-four–hour urinary sodium was positively related to LVM at baseline and at the end of the study, independently of age, sex, and systolic BP. Supine plasma aldosterone concentration was correlated with LVM only at baseline but not in multivariate analysis. In response to treatment, the percentage of change in LVM was positively correlated with the absolute changes in systolic BP, urinary sodium, and plasma aldosterone concentration, independently of baseline LVM. The population was divided into 3 tertiles according to final values of gender-specific urinary sodium. When, within each urinary sodium tertile, patients were divided into those with plasma aldosterone concentration below and above the median (11.6 ng/dL), LVMI progressively increased across sodium tertiles only in patients with high plasma aldosterone concentration. Systolic BP was similar across all of the groups. In conclusion, aldosterone requires the presence of high dietary salt for the expression of its unfavorable effect on the heart. (Hypertension. 2010;56:865-870.)

Key Words: left ventricular hypertrophy ■ sodium intake ■ hypertension ■ aldosterone ■ renin-angiotensin blockade

Although left ventricular hypertrophy (LVH) is considered as an adaptive mechanism that preserves cardiac pump function in the presence of pressure or volume overload, it also represents a preclinical disease strongly predictive of cardiovascular morbidity and mortality in hypertension. Moreover, some evidence indicates that reduction or volume overload, it also represents a preclinical disease strongly predictive of cardiovascular morbidity and mortality in hypertension. Moreover, some evidence indicates that reduction or aggravation of LVH, respectively, improves or enhances the risk of subsequent complications. In the Pressioni Arteriose Monitorate e Loro Associazioni cohort of 398 treated subjects with essential hypertension, a prevalence of LVH of 19% was found when adequate control (<140/90 mm Hg) of blood pressure (BP) was achieved, whereas the prevalence of LVH was 29% in the presence of uncontrolled BP. Because a number of treated patients exhibit levels of left ventricular mass (LVM) that exceed the need to sustain cardiac workload, it was suggested that nonhemodynamic factors may modulate or consistently influence the regression of LVH.

During the last decade, dietary sodium and aldosterone were shown to exert prohypertrophic effects on LVM, independent of their effects on BP. After the first observations obtained in a rather small number of patients, a positive influence of sodium intake on LVM (independent of sex and BP) was documented in most, albeit not all, large samples of subjects with never-treated hypertension. Furthermore, several studies conducted in hypertensive patients or in unselected populations observed a positive association between LVM and the circulating level of plasma aldosterone concentration (PAC), as well as urinary aldosterone excretion. Studies performed in animal models indicated that the pressor, proinflammatory, and profibrotic effects of exogenous aldosterone are observed in the presence of a high sodium intake and may be prevented by dietary sodium restriction. The effect of chronic reduction of dietary sodium on LVM has been rarely evaluated, and the respective influence of the decrease in BP and change in dietary sodium could not be clarified.

In a recent cross-sectional study conducted in patients with “resistant hypertension,” Pimenta et al observed that aldosterone excess and high dietary salt combine to sustain excessive urinary protein excretion. Whether such an interaction between aldosterone and dietary salt participated in the

Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz.

Received July 9, 2010; first decision July 29, 2010; revision accepted September 2, 2010.

From the Department of Internal Medicine, Centre Hospitalier Universitaire, Montpellier, France.

Correspondence to Albert Mimran, Department of Internal Medicine, Hôpital Lapeyronie, 34295 Montpellier Cedex 5, France. E-mail amimran@wanadoo.fr

© 2010 American Heart Association, Inc.

Hypertension is available at http://hyper.ahajournals.org

DOI: 10.1161/HYPERTENSIONAHA.110.159277

865
treatment-associated regression or resistance of LVH is unknown. The objective of the present study was to assess the concomitant influence of sodium intake and aldosterone, among other factors, on changes in LVM associated with long-term therapy by inhibitors of the renin-angiotensin system in never-treated essential hypertension.

Methods

Patients and Study Design

The study population consisted of 182 never-treated hypertensive subjects (38% women) aged 25 to 75 years. Patients with clinical evidence of atherosclerosis (stroke and coronary and peripheral artery disease), heart failure, renal failure (serum creatinine >130 μmol/L), diabetes mellitus (fasting blood glucose >6.7 mmol/L), marked obesity (body mass index ≥35 kg/m²), a history of alcohol abuse (>5 drinks per day), and secondary hypertension were excluded. To minimize the influence of physical activity on LVM, athletes (defined as a daily duration of physical activity of ≥1 hour) were not included in the study. Doppler echocardiography was performed in all to exclude patients with valvular lesions.

Subjects were evaluated at baseline and after a mean follow-up period of 35±9 months. No specific recommendation concerning dietary sodium restriction was provided. During follow-up, all of the patients were invited to repeat the clinical examination and echocardiography at least every year. All of the patients were treated with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor antagonist (ARA) given alone or in association with thiazide diuretics and/or calcium channel blockers and a β-receptor antagonist. None of the patients received furosemide, spironolactone, amiloride, or a combination of an ACEI and ARA.

BP and Urinary Excretion of Sodium Measurements

At every visit and in the morning, BP was measured every 3 minutes using an automatic device (model 8800, Colin Corp), and reported values are the average of ≥10 measurements after a 30-minute period of rest in the supine position. Hypertension was defined as systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg.

Subjects came to the ward with two 24-hour urine collections for the measurement of creatinine, sodium (as a marker of sodium intake), and potassium. To avoid inclusion of incomplete urine collections, subjects with a urinary excretion of creatinine <3 mmol/24 hours were excluded. In patients maintained in the supine position for ≥1 hour, blood was obtained for the measurement of glucose, electrolytes, and creatinine, as well as plasma renin activity and PAC (radioimunnoassay technique, CEA Sorin kit).

Echocardiographic Determinations

Echocardiographic assessment of LVM was performed by the same observer (G.d.C.) with an Acuson 128 XP10 or Sequoia (Acuson, Inc) with a 2.5- or 3.5-MHz transducer. Technical details were reported elsewhere. Tracings were analyzed using an offline station by 2 readers who had no knowledge of the patient’s clinical status. Measurement points were taken at the peak of the R wave on the simultaneous ECG, on an average of 3 cycles per recording. Interventricular septal thickness and posterior wall thickness at end diastole were measured according to the “Penn” convention. Relative wall thickness at end diastole was calculated as the ratio of twice the posterior wall thickness to left ventricular end-diastolic internal diameter. LVM was calculated by the Penn-cube method according to Devereux and Reichek. LVH was defined as LVM index (LVMI) >110 g/m² in women and 130 g/m² in men and concentric remodeling as relative wall thickness >0.43. Coefficients of variation of intrapatient and intraobserver variability for LVM measurement were, respectively, 9% and 8%.

Statistical Analysis

SPSS software (SPSS Inc) was used for statistical analysis. Differences in continuous variables between 2 groups were assessed by the Student t test for parametric data, and differences between categorical data were assessed by χ² analysis. Because of skewed distribution, plasma renin activity and PAC were log transformed before comparison of groups. Changes in systolic BP and LVM were the primary outcome parameters. The relationships between outcome parameters and potential predictors were first examined using linear univariate regression analysis. The change in BP during follow-up was also tested as a predictor of changes in LVM. Variables that exhibited significant univariate correlation with outcome parameters were then included in a linear multivariate regression analysis. To minimize the regression to the mean phenomenon, baseline values of cardiac parameters were always included in the multivariate model. When subjects were divided into tertiles of 24-hour urinary sodium excretion (UNaV), between-group comparison was performed by ANOVA and the χ² test (continuous and categorical variables, respectively). When ANOVA showed an overall significant difference, the Scheffe post hoc test was used for intragroup comparisons Two-tailed P<0.05 was considered statistically significant. Results are expressed as mean±SD.

Results

Clinical and Cardiac Parameters at Initial and Final Visits

During follow-up, patients were treated by ACEI or ARA (63% and 37% of the population, respectively) given alone or in association with diuretics in 61%, β-receptor antagonist in 26%, and calcium channel blockers in 27%. As shown in Table 1, in response to treatment, no significant changes in body weight, urinary excretion of sodium, and urinary excretion of potassium, as well as serum creatinine, sodium, and potassium concentrations were noted. A consistent decrease in systolic (by 13%) and diastolic (by 14%) BP was found, and satisfactory control (<140/90 mm Hg) was achieved in 64% of patients.

A significant decrease in LVMI (by 10%) and relative wall thickness was observed. In fact, the prevalence of LVH decreased from 56% to 39%, and this decrease was entirely due to a fall in concentric LVH from 46% of the whole population at baseline to 30% at the end of study. Normal LVMI with normal geometry was found in 21% of patients at baseline and increased to 34% in response to treatment. As

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Final</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>48±11</td>
<td>51±11</td>
<td>0.01</td>
</tr>
<tr>
<td>Body mass index, kg/m</td>
<td>26±4</td>
<td>26±4</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>164±18</td>
<td>142±17</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>98±11</td>
<td>84±11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>66±13</td>
<td>58±11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>67±9</td>
<td>66±10</td>
<td>NS</td>
</tr>
<tr>
<td>LVMI, g/m</td>
<td>131±42</td>
<td>118±30</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.48±0.12</td>
<td>0.46±0.10</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary sodium, mmol/24 h</td>
<td>155±60</td>
<td>154±67</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary potassium, mmol/24 h</td>
<td>83±28</td>
<td>84±31</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma renin activity, ng·mL⁻¹·h⁻¹</td>
<td>1.30±2.1</td>
<td>2.54±2.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Plasma aldosterone, ng/dL</td>
<td>15±9</td>
<td>14±8.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD. NS indicates not significant.

*Data show the t test basal vs follow-up.
compared with baseline, final plasma renin activity was higher, whereas PAC was unchanged.

**Determinants of Baseline and Final LVMI**

As shown in Table 2, the main determinants of LVMI at baseline and follow-up were age and systolic BP. UNaV was independently related to LVMI at baseline ($\beta=0.09; P<0.04$) and during follow-up ($\beta=0.07, P<0.002$). PAC was correlated to LVMI only at baseline in univariate ($r=0.18; P<0.002$) but not multivariate analysis. No influence of the type of antihypertensive therapy was detected.

The percentage of change in LVMI associated with therapy was positively correlated with the percentage of change in systolic BP, as well as the absolute changes in UNaV and PAC ($r=0.21, P<0.01$ and $r=0.32, P<0.01$, respectively). In multivariate analysis, this relationship remained significant, independent of baseline LVMI and the percentage of change in systolic BP. Inclusion of urinary potassium excretion in the model had no effect on the percentage of change in LVMI.

**Influence of Dietary Sodium and Aldosterone at End of Follow-Up**

The population was divided according to sex-specific tertiles of final UNaV. Across tertiles of UNaV, the proportion of patients receiving diuretics (only thiazides, as mentioned in the Method section) was similar (66% in tertile 1, 58% in tertile 2, and 59% in tertile 3). When, within each tertile of UNaV, patients were subdivided according to final PAC below ($\leq 11.6 \text{ ng/dL}$) and above ($>11.6 \text{ ng/dL}$) the median, no significant difference among the 3 groups was observed in systolic and diastolic BPs and age (Table 3). As shown in the Figure, LVMI progressively increased across tertiles of UNaV, only in patients with high PAC ($P$ for linear trend=0.03). In contrast, no sensitivity of LVMI to sodium was detected in patients with a final PAC of $<11.6 \text{ ng/dL}$. Of interest, within each sodium tertile, the proportion of patients maintained on diuretics was similar in subjects with final PAC below as compared with above median.

**Discussion**

In the present longitudinal study conducted in 182 never-treated patients with essential hypertension and LVH in 56% of subjects, long-term treatment (based on the use of ACEI in 63% and ARA in 37% of the population) was associated with a consistent decrease in LVMI after adjustment for age, sex, and baseline LVMI. The change in LVMI was correlated to the change in BP, as well as changes in 24-hour UNaV (reflecting a change in dietary sodium) and PAC. Before (as already demonstrated by several groups) and after treatment, LVMI was highly correlated to basal and final dietary sodium, independent of age, sex, and BP. At the end of follow-up, when the study group was divided into tertiles of sex-specific UNaV and then subdivided into those with a final PAC level above or below the median, it
was demonstrated that the combination of a high sodium intake with high PAC resulted in an increase in LVMI. Interestingly, in patients of the lowest tertile of sodium, no influence of the circulating level of aldosterone was detected. The main message of this study is that persistence of organ damage despite acceptable BP control (ie, <140/90 mm Hg in 64% of the population) may result from the combined adverse influences of excessive dietary sodium intake and breakthrough of aldosterone despite pharmacological blockade of the renin-angiotensin system.

Studies have established that echocardiographic LVM, to a better extent than BP, is an independent risk marker for cardiovascular complications in patients with essential hypertension. In addition, reduction in LVM resulting from BP control is associated with a marked reduction in cardiovascular events. Although the fall in BP is paralleled by a reduction in LVM, a stronger correlation between changes in 24-hour BP and changes in LVM (as compared with casual BP) was reported. In accordance with other studies, our results clearly suggest that, after adjustment for pretreatment LVMI, the most powerful determinant of LVMI reduction is the change in systolic BP resulting from treatment. Of interest, it was suggested by Devereux et al that the benefit of BP reduction on LV remodeling cannot be fully appreciated unless the duration of follow-up is ≥3 years (as in the present study).

In addition to systolic BP, other correctable determinants of LVM, such as overweight and sodium intake, have been identified. At a given level of BP, both LVM and albuminuria (another important marker of cardiovascular risk) were progressively higher in subjects with the highest level of sodium intake, as estimated by 24-hour UNaV. These observations were presently confirmed, because baseline and final LVMI were positively correlated with natriuresis, independent of systolic BP. To date, determination of 24-hour urinary excretion represents the best estimate of dietary salt, as compared with dietary recall and the sodium:creatinine ratio. In the present study, all of the patients received a treatment recommended for the treatment of hypertension. For a similar system (dual blockade was never proposed) given at doses conducted in patients in whom no advice about dietary salt was given, no change in UNaV estimated every 6 months and during a 24-month period of treatment by bendrofluazide was observed. In the same way, our results do not suggest any effect of long-duration (3-year) diuretic therapy on UNaV.

In the present study, 2 consecutive 24-hour urinary collections were obtained in patients instructed by our nurses to adequately collect urine. When patients were divided into tertiles of UNaV, the possibility of an interaction between salt appetite and diuretic administration (hydrochlorothiazide in all of the diuretic-receiving patients) could be raised. In a study conducted in patients in whom no advice about dietary salt was given, no change in UNaV estimated every 6 months and during a 24-month period of treatment by bendrofluazide was observed. In the same way, our results do not suggest any effect of long-duration (3-year) diuretic therapy on UNaV.

In our study, 2 consecutive 24-hour urinary collections were obtained in patients instructed by our nurses to adequately collect urine. When patients were divided into tertiles of UNaV, the possibility of an interaction between salt appetite and diuretic administration (hydrochlorothiazide in all of the diuretic-receiving patients) could be raised. In a study conducted in patients in whom no advice about dietary salt was given, no change in UNaV estimated every 6 months and during a 24-month period of treatment by bendrofluazide was observed. In the same way, our results do not suggest any effect of long-duration (3-year) diuretic therapy on UNaV.

In the present study, 2 consecutive 24-hour urinary collections were obtained in patients instructed by our nurses to adequately collect urine. When patients were divided into tertiles of UNaV, the possibility of an interaction between salt appetite and diuretic administration (hydrochlorothiazide in all of the diuretic-receiving patients) could be raised. In a study conducted in patients in whom no advice about dietary salt was given, no change in UNaV estimated every 6 months and during a 24-month period of treatment by bendrofluazide was observed. In the same way, our results do not suggest any effect of long-duration (3-year) diuretic therapy on UNaV.

In the present study, 2 consecutive 24-hour urinary collections were obtained in patients instructed by our nurses to adequately collect urine. When patients were divided into tertiles of UNaV, the possibility of an interaction between salt appetite and diuretic administration (hydrochlorothiazide in all of the diuretic-receiving patients) could be raised. In a study conducted in patients in whom no advice about dietary salt was given, no change in UNaV estimated every 6 months and during a 24-month period of treatment by bendrofluazide was observed. In the same way, our results do not suggest any effect of long-duration (3-year) diuretic therapy on UNaV.
patients, treatment was associated with normalization of BP in 64% and an overall significant decrease in LVM of ≈10%, corresponding with a decrease in the prevalence of LVH from 56% to 39% of the population. Multivariate analysis showed that the achieved change in LVM was positively correlated with the change in systolic BP and the changes in 24-hour UNaV and PAC, independent of baseline LVM, age, sex, and the type of antihypertensive treatment.

In essential hypertension, the influence of aldosterone on cardiac structure, as well as its response to treatment, has been markedly underestimated, especially in patients under pharmacological blockade of the renin-angiotensin system. The relationship between aldosterone and cardiac structure has mainly been evaluated in cross-sectional studies. In the Framingham cohort, consisting of an heterogeneous population of normotensive and hypertensive (treated and untreated) subjects, a positive correlation between plasma aldosterone (measured in a sample obtained after 30 minutes of rest in the supine position) and LVM was found only in women. In another study conducted in essential hypertensives off medication, the relationship between serum aldosterone and LVM was confined to obese black patients. In addition to its effect on tubular sodium handling, aldosterone has potent systemic and, more likely, local prohypertrophic and profibrotic deleterious properties. As reported by Brilla and Weber, the increase in BP, as well as interstitial and perivascular fibrosis induced by aldosterone infusion in rats, was prevented by dietary sodium restriction. Moreover, it was reported that long-term exposure of rats to a high sodium intake results in an increase in LVM associated with a marked increase in cardiac aldosterone synthase expression and aldosterone synthesis and angiotensin II type 1 receptor mRNA despite a drastic decrease in circulating renin and aldosterone. The demonstration of a role for aldosterone was reinforced by the observation that cardiac and renal abnormalities induced by long-term high sodium diet were corrected by spironolactone given during the last week of the study period.

In humans, evidence that dietary sodium impacts the effects of aldosterone is sparse. In a cross-sectional study conducted in 317 untreated subjects, Jin et al observed that LVM increased with sodium intake (estimated as 24-hour natriuresis) and was positively associated with urinary aldosterone (a better estimate of tissue exposure to aldosterone than plasma aldosterone). Such an observation is similar to findings obtained at baseline in the present cohort. Interestingly, observations of a similar association between microalbuminuria, considered as an important subclinical marker of organ damage induced by hypertension, and dietary sodium (estimated as urinary sodium:creatinine ratio) or serum aldosterone were reported by Fox et al.

The influence of dietary sodium on the relationship between LVM and aldosterone has not been properly assessed in follow-up studies in humans. In the present cohort, never-treated patients were investigated at baseline and after a 35-month period of treatment by blockers of the renin-angiotensin system at doses recommended in hypertension. In response to treatment, the supine level of plasma aldosterone was not different from baseline, whereas plasma renin activity increased. At the end of study, within each tertile of urinary sodium, LVM was higher in patients with final plasma aldosterone above the median, despite a similar BP level. This observation suggests that dietary sodium intake needs to be excessive to significantly enhance the effect of endogenous aldosterone on LVM.

In a cross-sectional study of 84 patients with resistant hypertension maintained on their usual treatment, Pimenta et al reported that urinary aldosterone and dietary sodium combined to enhance proteinuria without affecting BP. Aldosterone and dietary sodium may, thus, be considered as significant facilitators of the persistence or resistance of left ventricular abnormalities or proteinuria to BP reduction.

The lack of effect of chronic blockade of the renin-angiotensin system on plasma aldosterone deserves some comments. Some studies have shown that the long-term use of recommended doses of angiotensin II antagonists, such as losartan and irbesartan, had no effect on plasma aldosterone. In response to a 2- to 3-fold increase in the dose of the agent, a consistent reduction in plasma aldosterone associated with an additional decrease in albuminuria and no detectable fall in BP were observed. In patients receiving ACEI, PAC was shown to initially decrease and subsequently reach a level higher than baseline after a 6-month period of treatment. The finding of a lack of decrease of plasma aldosterone in some (~30% to 50%) patients chronically maintained on inhibitors of the renin-angiotensin system was defined as “aldosterone breakthrough” or “aldosterone escape” (no change or increase in plasma aldosterone). In patients with essential hypertension considered in a state of aldosterone breakthrough, no change or an increase in LV mass in response to treatment was observed. Unfortunately, no analysis of the influence of sodium intake was undertaken.

Perspectives

The weaknesses of the present study are mainly based on the use of plasma aldosterone instead of 24-hour urinary aldosterone, which is considered as a better estimate of integrated exposure to aldosterone. However, it is uncertain whether these parameters reflect the local activity of aldosterone. Unfortunately, the influence of the natriuretic peptide system (mainly the brain natriuretic peptide) on the relationship between aldosterone and dietary salt and changes in LVM was not assessed. It is possible that brain natriuretic peptide could act as a modulator or marker of the deleterious effects of salt and aldosterone (alone or combined) on the cardiac response to treatment in essential hypertension.

Among strengths of the study are the inclusion of patients with never-treated hypertension and the long duration of the study (35 months), the use of inhibitors of the renin-angiotensin system as the basis of therapy in all of the patients, and convincing evidence of an interaction between aldosterone and salt as a mechanism of resistance of LVH to these agents. The present findings may be a good basis for the treatment of patients with resistance of target organ damage to BP reduction. In such patients, drastic reduction in dietary sodium may represent an effective alternative, in addition to the use of aldosterone antagonists. With regard to the hypothesis that modest, population-wide reductions of dietary salt could be proposed to obtain a significant decrease in cardiovascular disease, our data suggest that the main benefits would be expected in the high-salt consumers.
Disclosures
None.

References
Dietary Sodium, Aldosterone, and Left Ventricular Mass Changes During Long-Term Inhibition of the Renin-Angiotensin System
Guilhem du Cailar, Pierre Fesler, Jean Ribstein and Albert Mimran

Hypertension. 2010;56:865-870; originally published online October 4, 2010;
doi: 10.1161/HYPERTENSIONAHA.110.159277

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/56/5/865

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/